REMARKS

Claims 25-62 are pending in the instant application, and claims 1-24 have been previously cancelled. Claims 55-62 have been withdrawn from consideration by the Examiner as non-elected subject matter. Thus, claims 25-54 have been examined according to the Office Action of August 17, 2007. The Office Action has asserted one of the following 3 rejections against claims 25-54: non-statutory obviousness-type double patenting, indefiniteness, lack of enablement, and/or unpatentable under 35 U.S.C. § 103.

Non-Statutory Double Patenting Rejection

Claims 25-28 have been rejected on the ground of non-statutory obviousness-type double patenting as purportedly being unpatentable over claims 20-24 in co-pending U.S Patent Application No. 10/532,320 ("the '320 Application"). Applicants respectfully traverse this rejection as pre-mature and citing an application that was filed after the instant application. Since claims 20-24 in the '320 Application have not been allowed, this rejection is premature, and should be a provisional double patenting rejection, at most. As of the date of this Amendment, claims 20-24 in the '320 Application have not been allowed. Furthermore, the '320 Application has an October 23, 2002 priority date, whereas the instant application has a July 12, 2002 priority date. A non-statutory obviousness-type double patenting rejection is not applicable to an application with an earlier filing date because a terminal disclaimer in the instant application would not disclaim any of the patent term. For these reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, Second Paragraph

Claim 25 has been rejected under 35 U.S.C § 112, second paragraph, as purportedly being indefinite due to its recitation of "precursors" in connection with the recitation of "when used in the present method." Applicants have deleted the recitation of "when used in the present method" as suggested by the Examiner. Accordingly, Applicants respectfully request that this rejection be withdrawn.

Claim 44 has been rejected under 35 U.S.C § 112, second paragraph, as purportedly being indefinite for its recitation of "an effective amount." Applicants respectfully traverse this rejection because a skilled artisan would understand the meaning of "an effective amount." A skilled artisan would know standard analytical techniques to determine the amount of a particular aromatase inhibitor needed to suppress blood serum 17β-estradiol levels to below 10 pg/ml in a subject. The standard analytical techniques do not require a great deal of experimentation to carry out a dosage-effect study to establish the minimum dosage of aromatase inhibitor that is required to reduce blood serum 17β-estradiol levels to below 10 pg/ml. For these reasons, a skilled artisan would understand the meaning of "an effective amount." Accordingly, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 112, First Paragraph

Claims 24-44 have been rejected under 35 U.S.C. § 112, first paragraph, as purportedly not enabling a skilled artisan to make or use the claimed invention. Particularly, the Office Action contends that the Specification does not enable a skilled artisan to prevent an estrogen-sensitive tumor and does not enable a skilled artisan to co-administer an effective amount of aromatase inhibitor. Thus, the Office Action concludes that claims 25-34 do not recite administering an aromatase inhibitor.

First, the Office Action asserts that claims 25-44 require the ***co-administration*** of aromatase inhibitor (see Office Action at page 7). However, claim 25 is directed to the administration of compounds having the claimed formulas or mixtures of one or more of the claimed formulas and/or their precursors. It does not require the co-administration of an amoratase inhibitor. In contrast, claim 35 is directed to administering the compound defined in claim 25 in combination with an aromatase inhibitor.

The Office Action further contends that claims 25-44 do not enable a skilled artisan to make and use the claimed invention because the Specification does not reasonably provide enablement for ***preventing*** the estrogen-sensitive tumors (Office Action at page 7). As discussed above, claims 25 and 35 have been amended to delete "preventing" and now recite "a method of

treating or prophylactically treating estrogen-sensitive tumours ...." Basis for this amendment can be found, for example, on page 13, lines 11-12 of the Specification. Accordingly, Applicants respectfully request that this rejection be withdrawn.

The Office Action also contends that the Specification fails to enable a skilled artisan to make and use an effective amount of aromatase inhibitor as recited in claim 44 (Office Action of page 7). To determine if a specification enables one skilled in the art to make and use the claimed invention, one must inquire whether the claimed invention can be practiced without undue experimentation. MPEP § 2164.01. That some experimentation may be required is not fatal because the issue is whether the experimentation is undue. *In re Vaeck*, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). There is no undue burden on a skilled artisan to determine the amount of a particular aromatase inhibitor that should be administered so as to suppress blood serum 17β-estradiol levels to below 10 pg/ml because a skilled artisan would be aware of standard analytical techniques available to make this determination. It would not require a great deal of experimentation to carry out a dosage-effect study to establish the minimum dosage of aromatase inhibitor that is required to reduce blood serum 17β-estradiol levels to below 10 pg/ml.

For these reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 103

Claims 25-28, 30-38, 40-48 and 50-54 have been rejected under 35 U.S.C. § 103 as purportedly being unpatentable over Elliesen (U.S. Patent Application No. 2002/0156059) in view of Holinka *et al.* (Biology of Reproduction, 1980, 22, 913-926). Applicants respectfully traverse this rejection because a skilled artisan would not reasonably expect that administering the recited formulas, instead of estriol, would treat or prophylactically treat estrogen-sensitive tumours prior to the filing of the instant application.

On page 17 of the Office Action, it is contended that Elliesen "teaches the use of a combination comprising an estrogen and an aromatase inhibitor for ***treating and reducing the risk of breast cancer***." However, in paragraph [0005], Elliesen recites that "the object of the invention was

therefore to provide pharmaceutical preparation that allow a long-term treatment in the form of an estrogen replacement therapy and in this case ***do not increase or even reduce the risk of breast cancer***." (Emphasis added). For references to obviate a claimed invention, they must teach, in combination, each and every element of the claimed invention. MPEP § 2112. In this case, Elliesen fails to teach a method for treating or prophylactically treating estrogen-sensitive tumours because, as stated in Elliesen, the composition taught in Elliesen does not "even reduce the risk of breast cancer." (Elliesen at ¶ [0005]). Thus, not only does Elliesen not teach a method for treating or prophylactically treating estrogen-sensitive tumours, it, in fact, teaches away from the claimed invention. This shortcoming is not overcome by Holinka *et al.* Therefore, the claimed invention is patentable over Elliesen in view of Holinka *et al.*

On page 15, the Office Action alleges that "Elliesen, J. also teaches that natural estrogens that have a longer action, such as estriol ... are particularly suitable (¶ 0020)." However, Elliesen (¶ 0020) has no bearing on the claimed formulas and is inaccurate with regard to estriol. While esters of estradiol have prolonged estrogenic activity, estriol is known as a short-acting estrogen.

On page 16, the Office Action acknowledges that "Elliesen, J. does not expressly teach the structure of an estrogenic compound, which contains up to four hydroxyl groups, such as estetrol ...." On page 17, the Office Action contends that it would have been obvious to a skilled artisan at the time of the invention to combine Elliesen's use of an oral form of estrogen and aromatase inhibitor with Holinka *et al.*'s purported teaching that estetrol has comparable estrogenic effect as other natural estrogens because estetrol is capable of stimulating uterine, and therefore, a skilled artisan would purportedly reasonably expect to successfully treat and reduce the risk of breast cancer because estetrol and estriol are structurally similar estrogens and have similar estrogenic properties. Applicants respectfully disagree with this contention because a skilled artisan would not reasonably expect to successfully treat or prophylactically treating estrogen-sensitive tumours in view of Elliesen and Holinka *et al.* because Holinka *et al.* do not teach a method of treating or prophylactically treating estrogen-sensitive tumours, nor do they teach that estetrol has comparable estrogenic effects as estriol. In fact, Holinka *et al.* teach the opposite -- that the estrogenic potency of

estetrol is low relative to estradiol and estriol.

Holinka *et al.* is directed to a study comparing the effects of estetrol and tamoxigen against estriol and estradiol on immature rat uteri. In the study, rats were injected with estetrol and tamoxifen subcutaneously, each day, at a dose of 50 μg per 100 g of bodyweight. Estradiol and estriol was administered at a dose of 1 μg per 100g bodyweight. The authors concluded that "on the basis of the present biochemical and morphological results, it is concluded that estetrol ("E4") and tamoxifen have estrogenic effects on immature rat uteri. However, ***the estrogenic potency of E4 relative to E2 or E3 was low at the dosage and timing of administration used in these experiments*** ...." "These results suggest that the conversation of E2 to E4 in the human fetus might represent an efficient mechanism of inactivation of the placental hormone." (Holinka *et al.*, abstract, emphasis added).

The portions of Holinka *et al.* cited above show that estetrol does not have comparable estrogenic effect as other natural estrogens, for example, estriol. The mere fact that estetrol is capable of stimulating uterine growth does not mean that estetrol has comparable estrogenic activity as natural estrogens such as estradiol and estriol. As Holinka *et al.* states, the estrogenic potency of estetrol (E4) is lower that estradiol (E2) or estriol (E3). Therefore, after considering the cited references, a skilled artisan would not have a reasonable expectation of success when combining the method described in Elliesen with the teachings in Holinka *et al.* because Holinka *et al.* fail to teach or provide any motivation or reason for a skilled artisan to employ estetrol instead of estriol since estetrol is described as having lower estrogenic activity as compared to estriol.

The conclusion stated in Holinka *et al.* – that estetrol has lower estrogenic activity as compared to estriol or estradiol – is in-line with observations made in other scientific literature. Copies of these references are enclosed with the accompanying Supplemental Information Disclose Statement. In sum, these references related to investigation of estrogenic potency of estetrol and conclude that estetrol is a weak estrogen. Moreover, Applicants are unaware of any recorded pharmaceutical use of estetrol up until the present invention.

Therefore, an artisan of ordinary skill in the field of steroids would not conclude from Holinka *et al.* that estriol and estetrol can be used interchangeably, be motivated to choose estetrol for an estrogen replacement method as described in Elliesen, or that the claimed formulas can be used in. Additionally, Elliesen viewed in combination with Holinka *et al.* does not teach a method of treating or prophylactically treating estrogen-sensitive tumours.

Claims 29, 39 and 49 have been rejected under 35 U.S.C. § 13 as purportedly being unpatentable over Elliesen in view of Holinka *et al.* in further view of Spicer *et al.* (U.S. Patent No. 5,340,584). Applicants respectfully traverse this rejection for the same reasons discussed above – because the Elliesen and Holinka *et al.* references fail to teach the claimed invention, and because there is no motivation to combine Elliesen and Holinka *et al.* or to use the claimed formulas instead of estriol or estridiol. In addition to these reasons, Applicants disagree that Spice *et al.* teach that estriol and estetrol can be used interchangeable with a reasonable expectation of success.

Spicer *et al.* is directed to a composition and method of inhibiting conception and treating gynecological disorders by administering gonadotropin hormone releasing hormone composition and an estrogenic composition, and therefore do not each, suggest or disclose a method of treating prophylactically treating estrogen-sensitive tumours. In column 7, lines 3-13, Spicer *et al.* recite

> Natural and synthetic estrogenic compositions which can be used according to the invention described herein include natural estrogenic hormones and congeners, including but not limited to estradiol, estradiol benzoate, estradiol cypionate, estradiol valerate, estrone, diethylstilbestrol, piperazine, estrone sulfat, ethinyl estradiol, mestranol, polyestradiol phosphate, estriol, estriol hemisuccinate, equinestrol, estropipate, pinestrol and estrone potassium sulfate. Equine estrongens, such as equilelinin, equilelinin sulfate and estetrol, may also be employed.

As discussed above, Applicants are unaware of any recorded pharmaceutical use of estetrol up until the present invention. Therefore, a skilled artisan would not reasonably expect to successfully use the claimed formulas instead of estriol. For a reference to either anticipate or make obvious a claimed invention, the reference must enable one skilled in the art to make and use the invention. MPEP § 2121. Even though estetrol is mentioned in Spicer *et al.*, Spicer *et al.* do not

enable one skilled in the art to use estetrol because a skilled artisan would not expect that estetrol to have estrogenic activity, as supported by the references discussed above and cited in the accompanying Supplemental Information Disclosure Statement. Consequently, one skilled in the art would not reasonably expect to successfully use the claimed formulas instead of estradiol.

Furthermore, Spicer *et al.* also fail to teach using estetrol in a method of treating or prophylactically treating estrogen-sensitive tumours. Since, as discussed above, neither Elliesen nor Holinka *et al.* teach such a method, the other cited references do not overcome Spicer *et al.*'s failure.

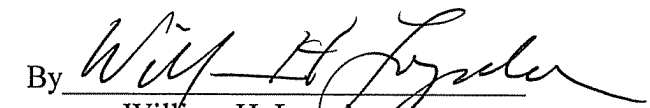
For these reasons, Applicants respectfully request that this rejection be reconsidered and withdrawn.

Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully submit that all pending claims in the instant application are patentable over the cited prior art and are in condition for allowance. Accordingly, reconsideration and withdrawal of the asserted rejections and a Notice of Allowance are respectfully requested. Should the Examiner have any questions or concerns, the Examiner is invited to contact Applicants' undersigned attorney by telephone at 412-471-8815.

Respectfully submitted,

THE WEBB LAW FIRM

By 

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